Environmental Health Perspectives
Vol. 101(Suppl. 1), p. 2 (1993)

Levels of Evidence of Carcinogenicity

The following information currently appears at the beginning of each Technical Report to inform the reader of the parameters used to classify the results.

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results *(Clear Evidence)* and *(Some Evidence)*; one category for uncertain findings *(Equivocal Evidence)*; one category for no observable effects *(No Evidence)*; and one category for experiments that because of major flaws cannot be evaluated *(Inadequate Study)*.

These categories of interpretative conclusions were first adopted by the National Toxicology Program in June 1983 and then revised in March 1986 for use in the NTP Technical Reports series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following quintet is selected to describe the findings. The categories refer to the strength of the experimental evidence and not to either potency or mechanism.

Clear Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemically-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

Equivocal Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

No Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing no chemically-related increases in malignant or benign neoplasms.

Inadequate Study of Carcinogenic Activity is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. This should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- The adequacy of the experimental design and conduct
- Occurrence of common versus uncommon neoplasia
- Progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions
- Some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant
- Combining benign and malignant tumor incidences known or thought to represent stages of progression in the same organ or tissue
- Latency in tumor induction
- Multiplicity in site-specific neoplasia
- Metastases
- Supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species)
- The presence or absence of dose relationships
- The statistical significance of the observed tumor increase
- The concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm
- Survival-adjusted analyses and false positive or false negative concerns
- Structure-activity correlations
- In some cases, genetic toxicology